Case Report

Therapeutic Exposure and Successful Response to Pembrolizumab in a Patient With Non–Small-Cell Lung Cancer Despite Significant Renal Loss Due to Paraneoplastic Nephrotic Syndrome

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Clinical Practice Points

- Discrepancies in pembrolizumab registration and its application in daily practice exist thanks to the sparse clinical data in specific patient populations.
- We report a case of non–small-cell lung cancer with paraneoplastic nephrotic syndrome in which therapeutic exposure and response were obtained despite renal loss of pembrolizumab.
- Determination of pembrolizumab serum concentrations can be helpful to ascertain therapeutic exposure.

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Introduction

Pembrolizumab is a humanized IgG4 anti–programmed cell death 1 (PD-1) antibody that is widely used in various malignancies. According to most recent European Society for Medical Oncology guidelines, pembrolizumab with or without chemotherapy is the standard first-line treatment option in stage IV non–small-cell lung cancer (NSCLC) patients without an actionable oncogenic driver.[1] Consequently, a major group of patients is treated with this immune checkpoint inhibitor that has significantly improved survival rates for a subgroup of patients.[2] Among these are patients with comorbid conditions, of which clinical data on pembrolizumab treatment are lacking because these patients are largely excluded from clinical trials.[3] This results in discrepancies between pembrolizumab registration and its application in daily practice.

Nephrotic syndrome is one of those comorbidities associated with lung cancer of which the impact on efficacy and safety of pembrolizumab therapy is unknown.[1,4] Nephrotic syndrome is characterized by severe proteinuria with hypoalbuminemia, hyperlipidemia, and peripheral edema,[5] conditions that interfere with monoclonal antibody pharmacokinetics. Proteinuria is known to cause renal excretion of therapeutic monoclonal antibodies, and hypoalbuminemia is reported to be correlated with an increase in monoclonal antibody clearance by enhanced protein turnover.[6] Pharmacokinetic measurements will give more insight in the impact of these conditions on immunotherapy exposure. Additionally, these findings underline the importance to report on treatment of patients in this setting to achieve safe and effective oncologic treatment.

We present a case describing the use, exposure, and outcome of pembrolizumab therapy to treat a case of NSCLC with proteinuria and severe hypoalbuminemia due to paraneoplastic nephrotic syndrome.

Case Report

A 55-year-old male patient was referred to our medical center for first-line immunotherapy treatment to treat a programmed death ligand 1 (PD-L1)-high stage IVA (cTxN3M1a) adenocarcinoma of

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the lung. PD-L1 expression was assessed by immunohistochemistry using a laboratory-developed technique based on detection of the primary antibody with a polymer type detection system and successfully cross-validated against the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies, Santa Clara, CA), resulting in a PD-L1 tumor proportion score of 90%. Next-generation sequencing did not reveal any options for first-line targeted therapy: there were no mutations in *EGFR, KRAS, BRAF, ERBB2*, or *MET*. Fluorescence in-situ hybridization (FISH) ruled out the presence of *ALK, ROS1*, or *RET* translocation. A significant amplification of *MET* (7 copies) was detected with FISH, which might be an option for treatment in a clinical trial after standard-of-care options have failed.

Approximately 4 months before tumor diagnosis, the patient experienced severe edema in his lower limbs and the lower parts of his abdomen. A peripheral arterial occlusion in the left leg was diagnosed, for which he underwent a percutaneous transluminal angioplasty and received antiplatelet treatment. The edema was attributed to vascular problems. During the analysis leading to the diagnosis of NSCLC, he experienced a deep venous thrombosis in his left leg, for which treatment with low-weight molecular heparin was initiated. A week after this event, radiologic and pathologic analysis established the diagnosis of metastasized NSCLC. He was referred to our hospital for treatment, where he was found to have pleural effusion, weight gain (~10 kg), dyspnea, cough, and thoracic pain. Complaints had greatly progressed in the last 3 weeks, leading to a severe deterioration of his fitness, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2. Pembrolizumab treatment was discussed and initiated 2 weeks later, after molecular analysis failed to show options for targeted therapy.

At this point in time, he was clinically diagnosed with nephrotic syndrome, with widespread edema, proteinuria (maximum 19.20 g/L), and hypoalbuminemia (lowest albumin 5 g/L; normal range, 35-50 g/L). Results for laboratory measurements over time are presented in Table 1. The ratio of IgG and transferrin clearance, the selectivity index, was increased (0.26, normal range: < 0.10), indicating the presence of a severe defect of the glomerular capillary filter. Serum anti−phospholipase A2 receptor and anti-THSD7A testing results were negative. A diagnosis of primary membranous nephropathy was thus considered unlikely, making a paraneoplastic syndrome the most probable underlying cause. Because the marginal performance status was mainly attributed to this paraneoplastic syndrome, treatment with first-line immunotherapy was started: 200 mg pembrolizumab intravenously every 3 weeks. Nephrotic syndrome was managed symptomatically, and edema decreased dramatically after initiation of amiloride. A kidney biopsy was initially not performed because of the high risk for hemorrhagic complications due to anticoagulant therapy, which could not be interrupted in the light of recent thromboembolic events and the high risk of recurrence. Moreover, the stable glomerular filtration rate and the absence of therapeutic consequences made histopathologic confirmation clinically less relevant.

Renal function loss and progressive hypoalbuminemia concurrent with radiologic evidence of NSCLC progression 12 months after the last pembrolizumab administration prompted us to perform a renal biopsy. Histopathology revealed a stage 2-3 membranous nephropathy, concordant with a paraneoplastic etiology.

Urinary loss of immunoglobulins in the setting of severe nephrotic syndrome raised concerns regarding pembrolizumab's therapeutic efficacy.[6] To evaluate this, serum and urine pembrolizumab levels were determined by enzyme-linked immunosorbent assay according to Pluim et al[7] (Table 1). Four, 6, and 9 weeks after the start of pembrolizumab treatment, serum trough concentrations (C_{min}) were 14.8 μg/mL, 78.8 μg/mL, and 73.1 μg/mL, respectively. Pembrolizumab peak plasma concentration (C_{max}) was 307 μg/mL six weeks after first administration. Urine pembrolizumab levels were assessed 4 and 6 weeks after first pembrolizumab administration and were 2.41 μg/mL and 1.63 μg/mL, respectively.

The patient's disease responded to immunotherapy treatment with a partial radiologic response: a maximum decrease of 33% in target lesion size according to Response Evaluation Criteria in Solid Tumors (RECIST) after 6 cycles of pembrolizumab treatment. His ECOG PS improved to 0. The edema resolved, and parameters associated with severity of the paraneoplastic nephrotic syndrome improved. The last available measurements during a stable disease state approximately 9 months after the first pembrolizumab administration showed a normal serum creatinine level (79 μmol/L), a serum albumin level that improved to 17 g/L, and a urine protein loss that decreased to 2.22 g/L. Pembrolizumab treatment was discontinued after 7 cycles because of therapy-related grade 4 neutropenia according to Common Terminology Criteria for Adverse Events (CTCAE) 4.03. More than 9 months (286 days) after the last pembrolizumab administration, the patient was seen with a tumor response that was characterized as stable disease according to RECIST.

Table 1 Results for Serum and Urine Drug Concentrations and Clinical Parameters for Nephrotic Syndrome by Time

Result	Time Since Start of Treatment						
	0 Weeks	3 Weeks	6 Weeks	9 Weeks	12 Weeks	24 Weeks	36 Weeks
Serum trough concentration pembrolizumab (μg/mL)		14.8	78.8	73.1			
Serum peak concentration pembrolizumab (μg/mL)			307				
Urine concentration pembrolizumab (μg/mL)			2.41	1.63			
Serum creatinine (μmol/L; normal range 60-110 μmol/L)	90	121	104	92	90	83	79
Serum albumin (g/L; normal range 35-50 g/L)	7	6	5	6	8	10	17
Urine protein (g/L)		19.20		15.72		17.48	2.22
Protein creatinine ratio (g/10 mmol; normal range < 10 g/10 mmol)		13.08				12.22	5.00

Informed consent for this case report was obtained from the patient.

Discussion

Despite severe hypoalbuminemia and significant renal pembrolizumab loss in our patient, therapeutic pembrolizumab serum levels and a clinical response to therapy were observed. The median expected C_{min} for pembrolizumab at a dose of 200 mg every 3 weeks is 27.6 μg/mL (10%-90% percentile, 14.9-46.2 μg/mL).[8] Early clinical studies of pembrolizumab used dosing strategies of 2 mg/kg every 3 weeks to 10 mg/kg every 2 weeks. It was found that maximum PD-1 inhibition by pembrolizumab is already achieved at doses of 1 mg/kg and higher, associated with a C_{min} in the range of 1-10 μg/mL.[9,10] Our patient obtained C_{min} levels above this concentration. The measured serum concentrations of our patient also fell well below expected concentrations at the highest explored dosage level in clinical studies that was found to be safe and tolerable (10%-90% percentile: 111.8-325.3 μg/mL and 315.9-599.9 μg/mL for C_{min} and C_{max}, respectively).[8] Obtaining therapeutic exposure was confirmed by the radiologic and clinical response and a significant improvement of the nephrotic syndrome.

In the absence of a renal condition, there is no renal loss of monoclonal antibodies because of impermeability of the renal glomeruli for molecules with high molecular mass.[11] However, proteinuria as occurs in paraneoplastic nephrotic syndrome is known to decrease the systemic exposure to therapeutic monoclonal antibodies.[6] Additionally, serum albumin concentrations have been reported to be inversely correlated with clearance of monoclonal antibodies through endogenous catabolism.[6] Hypoalbuminemia is associated with increased protein turnover and thus increased clearance and reduced systemic exposure to therapeutically administered monoclonal antibodies.[6] Urine pembrolizumab concentrations of our patient confirmed this.

Importantly, treatment with immune checkpoint inhibitors is associated with adverse renal effects, with tubulointerstitial nephritis being the predominant lesion.[12] Several reports have also described nephrotic syndrome in association with immune checkpoint inhibitor treatment.[13,14] However, on the basis of immunohistochemistry and molecular analysis, pembrolizumab was considered the best treatment option for our patient. Pembrolizumab treatment resulted in resolution of the nephrotic syndrome in parallel with the oncologic response. Our case thus demonstrates that anti−PD-1 treatment should not be withheld from patients with poor performance status due to suspected paraneoplastic nephrotic syndrome.

To our knowledge, there have been no previous reports similar to our case, where treatment with a monoclonal antibody in a patient with paraneoplastic nephrotic syndrome and both severe protein and monoclonal antibody loss resulted in therapeutic exposure and treatment response. A previous case report of a patient with paraneoplastic nephrotic syndrome in lung cancer described remission of nephrotic syndrome after adjuvant chemotherapy after resection.[15] The anti−PD-1 monoclonal antibody nivolumab was administered at recurrence of progression to metastatic disease. This resulted in complete remission. However, the nephrotic syndrome had already been resolved at the start of immunotherapy.

With this report, we hope to contribute to filling the information gap between clinical practice and clinical study data on the safety and efficacy of pembrolizumab, as patients with concomitant abnormalities or ECOG PS $\geq$ 2 are underrepresented in clinical studies.[2] Our case underlines the need for widening the inclusion criteria of clinical trials for novel anticancer drugs to better represent daily clinical reality. Furthermore, systematic collection and analysis of real-world data for approved drugs should be used to confirm the external validity of clinical trials, as has been previously advocated.[16-18]

Our case demonstrates the importance of an individual approach to oncologic treatment. On the basis of guidelines and low performance status, one might consider withholding this pembrolizumab treatment in this case. Our patient received therapeutic drug exposure and had disease that significantly responded to therapy. Therefore, clinicians may consider immunotherapy as a suitable anticancer treatment option in patients with paraneoplastic nephrotic syndrome. Determination of serum concentrations of monoclonal antibodies may help to ascertain whether therapeutic exposure is attained and help guide individual dose adjustments in case of severe proteinuria and hypoalbuminemia.

Conclusion

Despite renal loss of pembrolizumab in this NSCLC patient with paraneoplastic nephrotic syndrome, immunotherapy treatment resulted in therapeutic drug exposure and both radiologic and clinical response. As this is the first report in its kind, further studies to confirm efficacy of immunotherapy treatment in this setting are required. Determination of pembrolizumab serum levels can be helpful to establish if therapeutic exposure is attained in case of severe proteinuria and hypoalbuminemia. Clinicians should be aware that immunotherapy may still be an option in patients with these conditions, even with ECOG PS > 1. Despite reported renal adverse events of PD-1 inhibitors, including onset of nephrotic syndrome, our case report demonstrates that pembrolizumab can be an effective (palliative) treatment for patients with a PD-L1−high malignancy and paraneoplastic nephrotic syndrome.

Disclosure

The authors have stated that they have no conflict of interest.

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